

# Refractive index measurement using an optical cavity based biosensor with a differential detection

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## ABSTRACT

We proposed a low cost optical cavity based biosensor with a differential detection for point-of-care diagnosis. Two lasers at different wavelengths are used for the differential detection. This method enhances the sensitivity through higher responsivity and noise cancelation. To reduce noise further, especially due to the unstable low cost laser diode output, we employed a referencing method in which a reference pixel value in each CMOS image frame is subtracted from all other pixels. To validate the designed structure and demonstrate the sensitivity of it, we perform refractive index measurements of fluids with our design. In this presentation, we will discuss our design, simulation results, and measurement results.

**Keywords:** point-of-care, biosensor, optical cavity, differential detection, referencing method, noise cancelation, refractive index

## 1. INTRODUCTION

Early diagnosis of cancer and other chronic diseases dramatically decreases the death rate and treatment expenses.<sup>1</sup> A regular blood test is vital to detect the diseases in an early stage, however, current methods do not lend to early detection because of their high cost and inconvenience. Therefore, a point-of-care biosensor which is used for a low cost and convenient medical diagnosis near the patients has received much attention recently as a promising tool for early detection of diseases. A point-of-care device requires the following properties: label-free, low cost, high sensitivity, and high selectivity. Out of many proposed methods, optical biosensors such as surface plasmon resonance (SPR)<sup>2-3</sup>, optical fiber<sup>4</sup>, and optical cavity<sup>5-6</sup> based biosensor are attractive because of their label free operation, high sensitivity, and high selectivity. Among those optical biosensors, the optical cavity based biosensor is especially promising since it can be easily fabricated and integrated with a microfluidic system.

For an optical cavity based biosensor to be a successful platform for point-of-care diagnosis, a costly spectrometer and/or tunable laser cannot be used. To this end, we proposed a novel optical cavity based biosensor with a differential detection.<sup>7</sup> In this design, low cost laser diodes and a CMOS camera are used to detect the amount of biomarkers in a simple optical cavity structure using differential detection and noise reduction methods. Simultaneous detection of multiple biomarkers is also possible with this design. To validate the proposed design, we perform refractive index measurements of fluids with our design. In this paper, we will describe our design, simulation results for both bio-detection using a fixed index layer model<sup>8</sup> and refractive index change, and noise analysis. The measurement results of the refractive index measurement will be discussed in the presentation.

## 2. DESIGN AND SIMULATION RESULTS

A schematic of the proposed cavity based biosensor is shown in figure 1(A). Two collimated lasers at different wavelengths ( $\lambda_1=780\text{nm}$  and  $\lambda_2=850\text{nm}$ ) are expanded and combined at the beam splitter. Then, both wavelengths of light propagate through a rotating filter and the optical cavity. A CMOS camera is located at the end to detect the optical power of each wavelength. The optical cavity consists of two partially reflecting mirrors created by thin silver layers on both side of the cavity and a Polydimethylsiloxane (PDMS) layer on one side as shown in figure 1(B). Receptor molecules for target biomarkers are immobilized on the PDMS layer. Initially, the cavity is filled with a buffer fluid

with refractive index of 1.33. Afterward, a sample fluid with target biomarkers is introduced in the cavity. The biomarkers in the cavity adsorb to the surface and increase the sensing layer thickness. As the sensing layer thickness ( $\Delta d$ ) increases, the resonance curve will be shifted. We will measure intensity changes of two different wavelength lasers instead of the resonance curve shift which may require a costly spectrometer or tunable laser diodes. A computer programed system controls the rotating filter array to measure the optical power of each wavelength using a single CMOS camera.

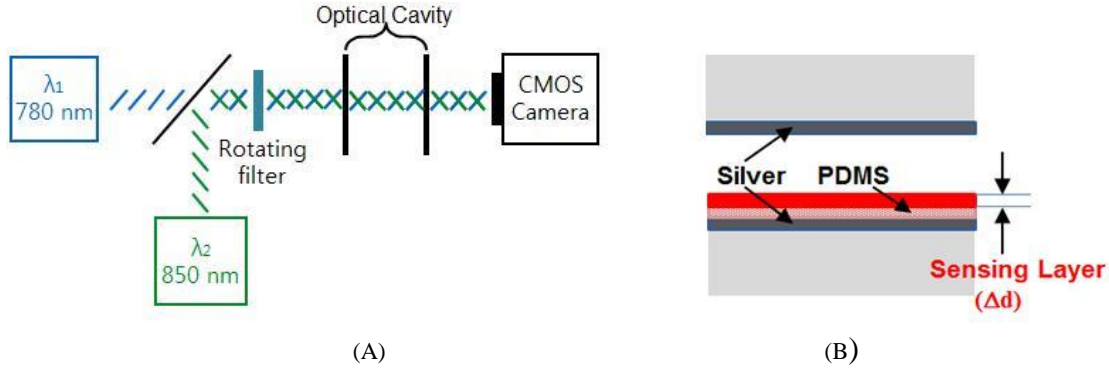


Figure 1. (A) Schematic of our biosensor design using two different wavelength laser diodes. (B) Cross-sectional view of an optical cavity structure.

To enhance the sensitivity of our design, we introduced a differential detection method. Optical intensities of two wavelengths are used to calculate a differential value using a scaled differential calculation shown below.

$$\eta = \frac{P_1 - (P_{10}/P_{20})P_2}{P_1 + (P_{10}/P_{20})P_2} \quad (1)$$

$\eta$  is the differential value,  $P_1$  and  $P_2$  are the optical power of  $\lambda_1$  and  $\lambda_2$  (two different wavelengths), and  $P_{10}$  and  $P_{20}$  are the initial values of  $P_1$  and  $P_2$ , respectively.

Using commercial software, FIMMWAVE/FIMMPROP (Photon Design), we optimized the structure to maximize the differential value change as the sensing layer thickness increases. The final cavity design has a  $2.53\mu\text{m}$  cavity width, 14nm silver layers on both sides, creating partially reflecting mirrors, and a 100nm PDMS (reflective index = 1.412) layer on one side.

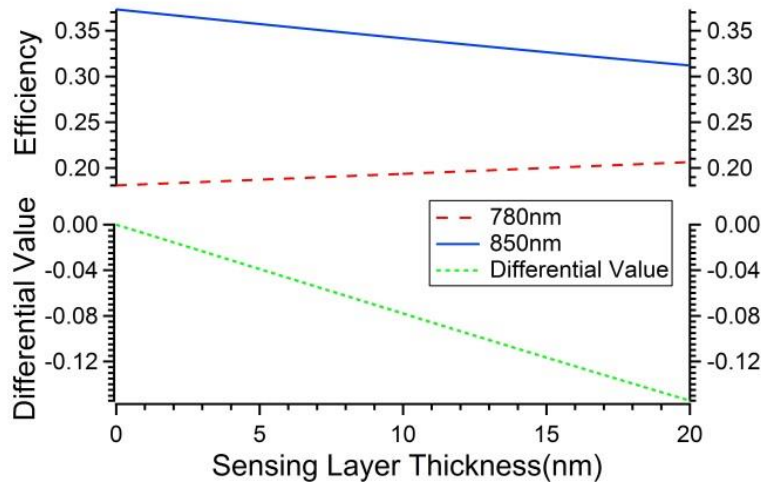


Figure 2. Differential value and efficiencies of individual wavelengths vs. sensing layer thickness

Figure 2 shows the efficiencies of individual wavelengths and the differential value as a function of sensing layer thickness. As the sensing layer thickness increases from 0 to 20nm, the efficiency of the 780nm laser increases from 0.181 to 0.206( $\Delta P_1 = 0.025$ ) while that of the 850nm laser decreases from 0.373 to 0.312( $\Delta P_2 = 0.061$ ). Because these efficiencies change linearly with opposite slope, the calculated differential values show a much larger change. For the same sensing layer thickness change, the differential value begins at 0 and linearly decreases to -0.154( $\Delta \eta = 0.154$ ), more than two times larger than that of an individual wavelength. This larger change in differential value leads to an enhanced sensitivity of this cavity based biosensor. We also anticipate that the scaled differential calculation will cancel out the common noise along the propagation path because both travel the same path and the differential value is calculated by the difference.

Even though we anticipate an intrinsic noise reduction characteristic from the scaled differential calculation methods, significant noise is still detected from the low cost laser diodes and CMOS camera. To reduce noises further, we employed a referencing method which normalizes the measured value with respect to a reference value. The equation used for the referencing method is as follows.

$$S = S_{D\_data} - S_{D\_ref} \times \frac{S_{I\_data}}{S_{I\_ref}} + S_{I\_data} \quad (2)$$

$S$  is the calculated value,  $S_{D\_data}$  is a pixel values in a data frame,  $S_{D\_ref}$  is the reference value in the data frame,  $S_{I\_data}$  and  $S_{I\_ref}$  are the data pixel and reference pixel value in the initial frame respectively as shown in figure 3(A). The initial frame is the first frame collected by the CMOS camera. Figure 3(B) shows the intensity data of the 780nm laser collected at a pixel of the CMOS array for 40 minutes. As shown in the figure, the measured signal is very noisy having an average of 158.82 with a standard deviation of 11.289. After normalization of the raw signal of the 780nm laser using the referencing method, the standard deviation is improved significantly as shown in Figure 3(C). The normalized signal has an average of 158.824 with a standard deviation of 2.707.

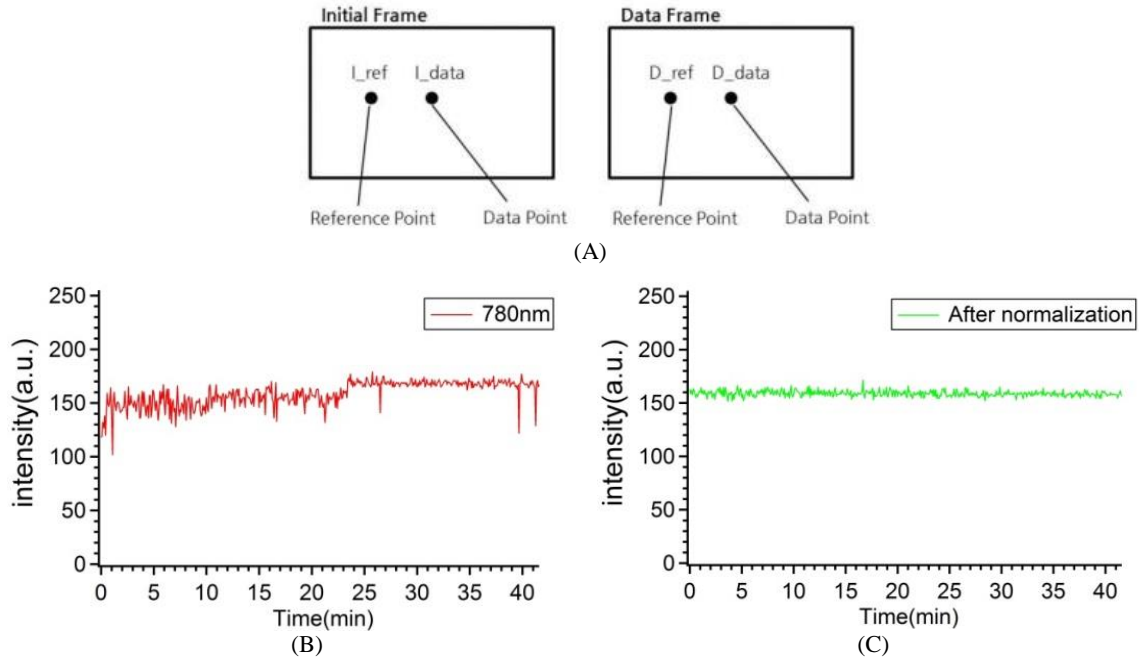


Figure 3. (A) Location of data and reference pixels. (B) Intensity of 780nm laser diodes for 40 minutes. (C) Intensity of normalized 780nm laser diode.

To demonstrate enhanced sensitivity with the differential detection and noise reduction methods, we perform refractive index measurements. We simulated the efficiency and differential value changes for different refractive index of fluids in the cavity. Figure 4(A) shows the efficiencies of the 780nm and 850nm wavelengths as a function of fluid index changing from 1.30 to 1.50 while the differential value changes are shown in Figure 4(B). In the range of fluid index

from 1.32 to 1.35, two optical powers have the most opposite and monotonous changes which in turn lead to the largest differential value change. In this region, the differential value change is equivalent to  $-48.41 \pm 0.63$  / R.I.U. (refractive index unit). Based on the measured average noise of the differential value, we anticipate to accomplish a limit of detection of  $86.33 \times 10^{-6}$  R.I.U. over the range 1.32 to 1.35. The fabrication of the device and measurements are underway. The latest measurement results will be presented at the conference.

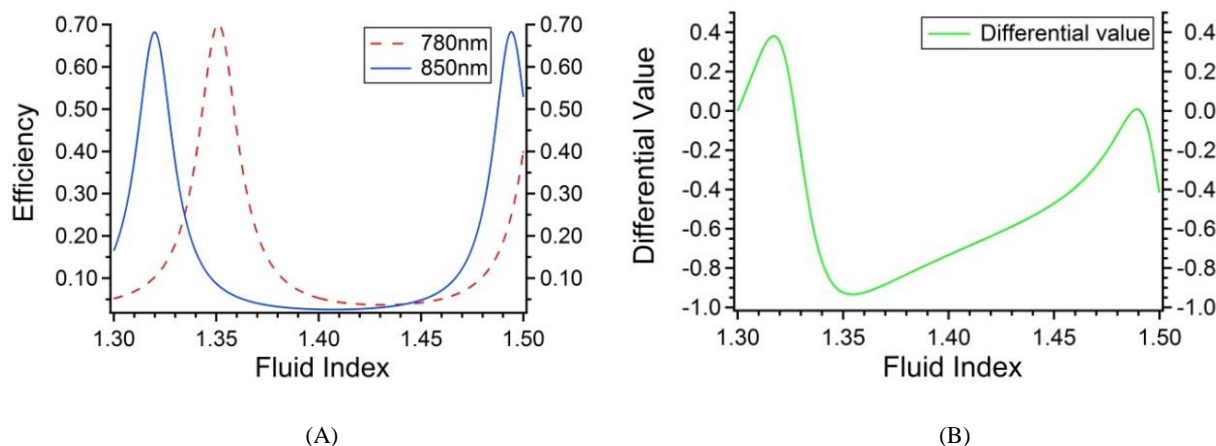


Figure 4. (A) Efficiency of individual laser as fluid index changes. (B) Differential value as fluid index changes.

### 3. CONCLUSION

We proposed an optical cavity based biosensor with differential detection toward point-of-care diagnosis. Through the differential detection method, the sensitivity is enhanced and a certain common noise between the two wavelengths along the propagation path is expected to be canceled out. We employed a referencing method to further suppress the noise and showed significant improvement. Refractive index measurements are chosen for the demonstration of the enhanced sensitivity and noise reduction methods. The limit of detection of  $86.33 \times 10^{-6}$  R.I.U. over the range of refractive index from 1.32 to 1.35 is expected from the simulation results and measured average noise of detection system. The fabrication of the device and measurements are underway. The latest measurement results will be presented at the conference.

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